REMARKS

With the entry of the present Amendment, claims 51-63 and 66-93 are in this application. Claim 62 has been amended to add the limitation from claim 64, which has been canceled without prejudice. Claims 69, 79 and 91 have been amended to better claim the invention. New claims 92-93 are presented, with support found in as-filed claim 90. Claim 90 has been amended to delete recitation of Theracyte, which has been replaced with a "subcutaneous implant device which is impermeable to cells but permeable to proteins." Support is found at page 24, lines 19-23. Claim 90 has been amended to be independent, incorporating the limitations of claims 62 and 89. Claim 91 has been amended to depend from claim 90 rather than from 89. Claim 52 and the Specification have been amended to correct an obvious typographical error. None of the amendments made herein constitutes the addition of new matter.

The Information Disclosure Statement

The Examiner has not considered a Chinese language reference because there was no date shown. Submitted herewith is a Supplemental Information Disclosure Statement (with fee as required by 37 C.F.R. 1.17(p)) that provides the date of the re-submitted material, as indicated by Applicants to the undersigned. Consideration is respectfully requested.

The Objections to the Claims

Claim 79 is objected to for reciting a Markush type species, and the Examiner has suggested the use of "selected from the group consisting of ...."

Applicants respectfully urge that the Examiner reconsider the objection to claim 79. The MPEP at 2173(h) states as follows:

> When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively.

For example, if "wherein R is a material selected from the group consisting of A, B, C and D" is a proper limitation, then "wherein R is A, B, C or D" shall also be considered proper.

Claim 91 is objected to for reciting method rather than device. In the interest of advancing prosecution, Applicants have amended claim 91 for consistency with the claim from which it depends.

The Rejections under 35 U.S.C. 112, second paragraph

Claims 64, 69 and 90 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite.

Claim 64 is said to recite "the hepatocyte cells are from immortalized cells in a commercially available culture. " The Patent Office has alleged that it is unclear whether the hepatocytes are derived from a commercially available culture, the hepatocytes are the immortalized culture or the hepatocytes are immortalized in a commercially available culture medium.

Claim 64 has been canceled without prejudice in the present Amendment. Accordingly, this aspect of the rejection is now moot.

Claim 69 is said to recite a ratio between gall bladder:hepatocytes, and that it is unclear whether this ratio is based on number of cells or other parameters. Clarification is required.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 69 to recite ... a ratio of "cells of" between 0.5:2 and 2:0.5 gall bladder epithelial cells:hepatocytes"... Applicants respectfully submit that the claim as amended meets the requirements of the statute for clarity and that original claim would be understood by the skilled artisan to mean a ratio of cell numbers.

Claim 90 is noted to recite a trademark or trade name. Additionally, claim 90 is said to recite the phrase "such as", which allegedly renders the claim indefinite.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have deleted the recitation of "such as" and "Theracyte" and add recitation of "subcutaneous implantation device which is impermeable to cells and permeable to proteins and secreted factors." Support is found at page 24, lines 19-23.

The Rejections under 35 U.S.C. 112, first paragraph

Claims 62-75 and 89-01 have been rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The amendment of claim 62 to recite "differentiated" is allegedly new matter.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 62 to delete the recitation of "differentiated" and replace it with "wherein said cell type maintains its cell phenotype". Support is found at page 23, lines 19-20 and 22-25, page 24, lines 5-6, page 25, lines 3-5, and at Example 2 of the as-filed Specification.

The Rejections under 35 U.S.C. 102

Claims 62, 66-68 and 70-74 have been rejected under 35 U.S.C. 102(b) as allegedly unpatentable over Kobayashi (1991) Gastroentelogica Japonica or Lee et al. (2003) Am. J. Physiol. Gastrointest. Liver Physiol. Applicants respectfully traverse this rejection.

The cited references are each said to teach a culture of human gall bladder epithelial cells. The Patent Office has indicated that the stated intended use of the

claimed compositions (for implantation) has no weight. The Patent Office has further stated that "the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's function, does not render the old composition patentably new to the discoverer".

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 62 to recite neonatal non-hepatocyte cell type.

Applicants respectfully maintain the Kobayashi describes a cell culture protocol but not an implantable composition of gall bladder epithelial cells. As reported at page 367, first paragraph, the GBEC were cultured for 5 days until growth was confluent, and the cells were then detached from the culture plates but could not be subcultured further and only survived an additional 7 days in the new culture dish. Such cells are not suitable for implantation, and this is certainly appreciated by one of ordinary skill in the relevant art. Moreover, the Kobayashi reference indicates that the GBEC were derived from material removed from patients with bladder stones. Nowhere does the cited Kobayashi reference state that the patients were neonates.

The cited Lee reference describes secretion of apoA-I and apoA-E from cultures canine GBECs. Again, the paper merely discloses the *in vitro* culture of canine GBECs, with no suggestion or disclosure that the cells could be implanted. Nowhere does the cited Lee reference state that the cultured cells were neonatal GBECs.

In view of the foregoing, Applicants respectfully submit that the present claimed invention is not anticipated by either the cited Kobayashi reference or the cited Lee reference. Accordingly, the withdrawal of the rejection is requested.

Claims 62-63, 66-68 70-75 and 89 have been rejected under 35 U.S.C. 102(b) as allegedly unpatentable over Clement et al. (1984) Hepatology. Applicants respectfully traverse this rejection.

The Patent Office has interpreted the present claimed compositions as comprising hepatocytes and gall bladder epithelial cells. Clement is said to teach a co-culture system comprising hepatocytes and gall bladder epithelial cells. Again, the Patent Office indicated that the stated intended use of the claimed compositions (for implantation) has no weight.

The cited Clement reference describes a co-culture system of human hepatocytes with rat liver epithelial cells, wherein the RLECs enhance deposition of extracellular material (EM) around the hepatocytes. EM deposition enables the hepatocytes to survive in culture for longer periods and to actively secrete albumin for longer periods. No such EM deposition was observed when human hepatocytes were cultures with human GBECs. Neither did the co-culture system appear to enhance cell survival or albumin secretion.

As noted above, claim 62 has been amended to recite that the non-hepatocyte cells are neonatal cells. In fact, the Clement reference states that GBECs were derived from human kidney donors or bovine lens. Nowhere does the cited Clement reference state that the non-hepatocytes are neonatal in origin.

With respect to claim 89, it is drawn to an implantable device. There appears to be no teaching of any implantable device in the cited Clement reference.

In view of the amendments to the claims and the arguments advanced herein above, the claimed invention is not anticipated by the cited Clement reference, and Applicants respectfully request that the rejection be withdrawn.

The Rejections under 35 U.S.C. 103

Claims 62-75 and 89 and 91 have been rejected under 35 U.S.C. 103(a), as allegedly unpatentable over Clement in view of Kobayashi et al. (2001) Addition Biology, Abstract only. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 91 to depend from claim 90; thus it is believed to be allowable.

Applicants respectfully maintain that Clement and Kobayashi merely teach an *in vitro* culture system, and neither teaches nor suggests that such cultured cells would be useful as an implantable composition to provide one or more liver metabolic and/or physiologic functions to said recipient comprising non-hepatocyte cells only as claimed in claim 62. Neither does either the cited Clement reference nor the cited Kobayashi abstract teach the use of neonatal non-hepatocytes in their cell compositions. However, the Examiner has taken the position that neonatal material was an obvious selection from the finite number of identified sources of gall bladder epithelial cells.

Furthermore, neither of the cited references appear to teach or suggest that that non-hepatocytes have the ability to express proteins that are characteristically expressed by hepatocytes so that the claimed compositions could be implanted into a subject with either a disease or a congenital deficiency and have levels of proteins expressed by the implanted cells that would rectify the deficit associated with the disease or deficiency.

Kobayashi appears to describe an *in vitro* system for human gall bladder epithelial cells which did not survive for long periods in cell culture (5 days, with survival for 7 more days but unable to be subcultured). Clement describes a co-culture system of human hepatocytes and RLECs. When Clement replaced the RLEC with human BGECs, the human hepatocytes did not have extended cell survival rate or enhanced

albumin secretion. One of ordinary skill in the art, reading Clement, would not be moved substitute GBEC for the RLEC. Therefore, the two references do not appear to be appropriately combined in the rejection because, from the teachings of the Kobayashi abstract and the Clement reference, one would actually expect a co-culture that was not suitable for implantation for therapy in that there was no extended survival of human hepatocytes *in vitro* and one would not expect extended survival after implantation either. By contrast, the present disclosure provides for a synergistic effect of hepatocytes on the secretion of Factor VIII, an exemplary liver secreted protein, from non-hepatocytes. These unexpected results of present Applicants could not have been predicted from the teachings of the cited references.

Applicants respectfully point out that that Clement et al. alone teaches the use of human hepatocytes and rat liver epithelial cells, where **only the hepatocytes** secrete liver secretory factors such as albumin. The RLEC are an essential feature of the *in vitro* co-culture system of Clement to produce the extracellular matrix that appears to protect the hepatocytes and maintain the structure and function in vitro. One of ordinary skill in the art would, not from the teachings of Clement et al. and Kobayashi be motivated to either use RLEC only as a possible implant to provide liver secretory factors to a recipient or to use human GBEC only or a co-culture to provide liver secretory factors to a recipient, for example as part of an implantable composition, as taught and claimed in the present application.

In view of the foregoing discussion, Applicants respectfully maintain that the present claimed invention is not *prima facie* obvious over the cited references, and thus, the reference should be withdrawn.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

It is believed that this amendment does not necessitate the payment of any fees pursuant to 37 C.F.R. 1.16- 1.17. If this incorrect, please charge any fees due pursuant to the foregoing Rules and grant any extension of time, if necessary, to Deposit Account No. 07-1969.

Respectfully submitted,

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